

HIV TRANSMISSION TO PREMATURE VERY LOW BIRTH WEIGHT INFANTS

By

Candyce Levin

LVNCAN001

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Supervisor: Dr Lloyd Tooke

Groote Schuur hospital Neonatology

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1. List of abbreviations

GSH	Groote Schuur Hospital
NSH	New Somerset Hospital
VLBW	Very low birth weight
AZT	Zidovudine
NVP	Nevirapine
NHLS	National Health Laboratory Service

2. Acknowledgements and contributions

Dr Candyce Levin, Paediatric registrar at Red Cross War Memorial Childrens Hospital.
Principal researcher, protocol development, data collection and manuscript preparation.

Dr David M Le Roux, Paediatric consultant New Somerset hospital. He assisted with data collection from NSH and reviewed the manuscript.

Professor Michael C Harrison, Head of department of neonatology at Groote Schuur hospital.
He assisted with the development of the protocol and reviewed the manuscript.

Dr Lloyd Tooke , Neonatologist Groote Schuur hospital. He assisted with the design of the protocol and with drafting and design of the article.

3. Published journal article

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Follows on next page.

HIV Transmission to Premature Very Low Birth Weight Infants

Candyce Levin, MB ChB, DCH, David M. Le Roux, MB ChB, FCPaed, Cert ID(SA) Paeds,† Michael C. Harrison, MB ChB, MRCP, FRCPCH,*‡ and Lloyd Tooke, MB ChB, FCPaed, MMed(Paed), Cert Neonatology(SA)*‡*

Abstract: There is sparse literature about HIV transmission in preterm infants. Eighty-two HIV-exposed preterm infants received birth polymerase chain reactions (PCRs). Five (6.1%) were HIV positive with all 5 mothers receiving inadequate antiretrovirals. Of the PCR-negative infants, 9 died and 87% of the survivors received further PCR testing which remained negative. With correct care, intrapartum transmission of HIV can virtually be eliminated.

Key Words: prematurity, HIV transmission, prevention of mother to child transmission, very low birth weight, neonatal

Preterm birth (born before 37 completed weeks) is associated with higher risk of perinatal HIV transmission, especially for those born before 33 weeks.^{1–3} However, there is limited information about HIV-exposed preterm infants, especially those with very low birth weight (VLBW) (<1500 g). One reason for this may be that in countries with high HIV prevalence, neonatal mortality rates are also high, and these small infants often do not survive.⁴ Treatment and prevention of HIV in premature infants have been termed “the last and first frontiers.”⁵

We have previously shown that it is possible to achieve a low risk of transmission 2.7% (0.7%–14.1%) in extremely low birth weight HIV-exposed infants (<1000 g).⁶ However, this study was limited by the lack of determination of HIV status in the 27% (14/51) of infants who died before the 6-week HIV testing.

The objective of this study was to describe the characteristics and outcomes of a cohort of HIV-exposed VLBW infants.

METHODS

From August 2014 to April 2015, we prospectively enrolled into a database all VLBW babies born at Groote Schuur Hospital (GSH) and New Somerset Hospital (NSH) in Cape Town, South Africa. GSH, one of 2 government tertiary referral centers for the Western Cape Province, delivers about 460 VLBW infants per year, and approximately 40% of these are delivered because of maternal severe pre-eclampsia/hypertension causing maternal or fetal compromise.⁷ NSH is a secondary hospital with about 160 VLBW infants per year.

HIV prevalence in pregnant women is approximately 16%.⁶ Mothers who are not tested for HIV during pregnancy are tested soon after birth. According to provincial protocols, women who test positive during pregnancy are started on triple therapy (once daily fixed dose combination: efavirenz, 600 mg; emtricitabine, 200 mg and tenofovir disoproxil fumarate, 300 mg). During labor, mothers who are known to be HIV positive but not receiving antiretrovirals (ARVs) at the time of delivery are given prophylaxis, which includes nevirapine, zidovudine and tenofovir disoproxil fumarate/ emtricitabine. All premature infants are considered high risk of HIV infection regardless of the maternal viral load and are thus started on dual prophylaxis (4 weeks of zidovudine 2 mg/kg twice daily) and at least 6 weeks of nevirapine (2 mg/kg daily for 2 weeks and then 4 mg/kg daily thereafter). Exclusive breastmilk is encouraged for most babies because of its many benefits and the small risk of transmission, especially if the mother’s viral load is low.⁸

However, because of concerns of possible increased transmission in the premature baby, mother’s own milk, if it was available, was pasteurized before administration until she could breastfeed directly. If there was insufficient mother’s milk, the infants either received pasteurized donated milk if they weighed <1200 g or formula if they were >1200 g. The weight cut off was necessitated by limited donor milk stocks.

Information was abstracted from medical records into an Excel database, including maternal ARVs, viral load, comorbidities, pregnancy and delivery outcomes, infant birth weight, estimated gestational age, clinical course, feeding, ARV history and HIV testing results. The polymerase chain reaction (PCR) assay used for infant HIV testing was Roche Cobas Ampliprep/Cobas TaqMan (CAP/CTM), which detects both DNA and RNA. Approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee was obtained for the maintenance of this database.

RESULTS

Eighty-four VLBW infants (77 at GSH and 7 at NSH) were born to 79 women with HIV infection during that period. No infants were excluded from the study. Of the 79 women, 17 (22%) received no antenatal care, and 25 (32%) were diagnosed with HIV during the pregnancy or after delivery. Fifty-seven women (72%) received ARVs at least 1 month before delivery, while 7 (9%) received less than 30 days ARV treatment. Ten women (13%) received no ARVs at all before delivery, and for 5 (6%), the duration of ARV use was unknown. Viral load was undetectable in 37 women (47%), unknown in 25 (32%), <log3 in 4 (5%) and >log3 in 13 (16%).

The infant weights, gestational ages, mode of delivery and deaths are depicted in Figure 1. Twelve babies died before discharge home (2 of these on the first day of life before PCR testing was done). The deaths were predominantly in the babies less than 1000 g, and the overall survival rate (85%) was similar to our background VLBW survival rate (83%). Most of the deliveries (57%) were by cesarean section without labor due to complications of PET.

Of the 84 infants, 82 had an HIV PCR test performed within 48 hours of birth, of which 5 (6%) were PCR positive. All 5 mothers had received either no ARVs² or suboptimal antiretroviral therapy duration of 2, 4 or 8 weeks. In all cases, the infants' dual prophylaxis was converted to triple antiretroviral therapy (zidovudine, lamivudine and nevirapine) within 10 days of life. One infant died on day 34 from necrotizing enterocolitis; 3 infants achieved virologic suppression, and 1 did not Table 1.

None of the infants who were PCR negative at birth tested positive at either 6 weeks (87% tested) or 10 weeks (49% tested). Feeding at discharge from GSH and NSH was exclusive breastfeeding 51 (71%), exclusive formula feeding 12 (16%), mixed feeding 7 (10%) and unknown 2 (3%).

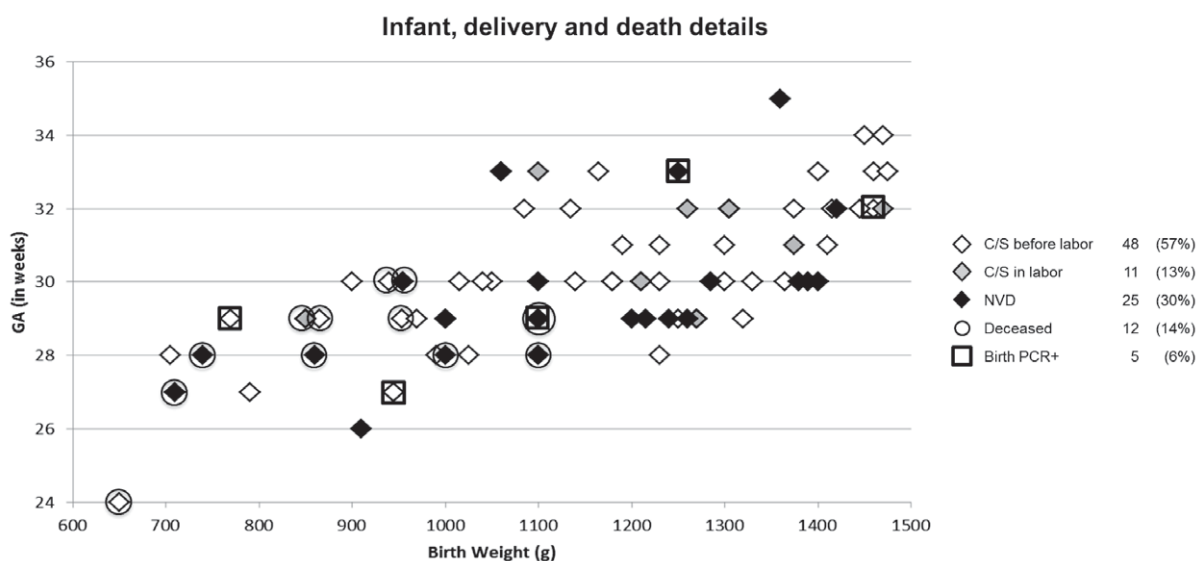


FIGURE 1. Weight, gestational age, mode of delivery and outcome of HIV-exposed infants. C/S indicates cesarean section; GA, gestational age; NVD, normal vertex delivery.

TABLE 1. Characteristics and Outcomes of HIV-infected VLBW Babies

Clinical variables	Baby 1	Baby 2	Baby 3	Baby 4	Baby 5
Maternal antiretroviral therapy	None	None	2 wk before delivery	4 wk before delivery	8 wk before delivery
Maternal viral load	Log 3.4	Unknown	Unknown	Log 4.2	146
Maternal CD4	195	537	522	116	168
Maternal HIV diagnosis	Before pregnancy	Postpartum	In this pregnancy	In this pregnancy	In this pregnancy
Mode of delivery	NVD	C/S before labor	NVD	C/S before labor	C/S before labor
Indication for delivery	Spontaneous preterm labor	Pre-eclampsia with fetal distress	Induction of labor for pre-eclampsia	Chorioamnionitis	Pre-eclampsia with fetal distress
Birth weight	1100	770	1250	950	1460
Gestational age	29	29	32	30	32
Gestation age scoring	Ballard	Ballard	Ballard	Early ultrasound	Ballard
Age at PCR testing	D1	D1	D1	D1	D1
Age at commencement of triple ART	D5	D6	D6	D7	D10
Duration of follow-up	34 d	8 mo	6 mo	4 mo	9 mo
Outcome	Died of NEC on day 34	LDL viral load Moved back to Zimbabwe	Good growth but unsuppressed viral load	LDL viral load Transferred to district services	LDL viral load Transferred to district services

ART indicates antiretroviral treatment; C/S, cesarean section; LDL, lower than detectable limit; NEC, necrotizing enterocolitis; NVD, normal vertex delivery.

DISCUSSION

Mother-to-child transmission of HIV can occur during pregnancy, intrapartum or through breastfeeding. Of these 3 mechanisms, there is evidence that preterm birth differentially affects the risk of intrauterine and intrapartum transmissions.

One of the only advantages to being born preterm is that this decreases exposure time to contract intrauterine HIV. The intrauterine transmission rate for infants born to untreated HIV-infected mothers has been reported to be 1.6% at 28-weeks and 5.1% at 36-weeks gestation.⁹ Barriers such as skin and mucous membranes are thinner and more friable than in term infants, increasing the risk of transmission when these infants are exposed to conditions such as chorioamnionitis, prolonged rupture of membranes or vaginal birth.¹⁰

As maternal viral load is the strongest independent predictor of transmission,^{11,12} preterm infants are also disadvantaged if their mothers are diagnosed or started on treatment during pregnancy as there is less time before birth to achieve virologic suppression.

Intrauterine transmission in our cohort was higher than expected at 6.1%. All 5 of these pregnancies however could classify as high risk as ARVs were started very late or not at all. Of the 4 who survived to discharge, 3 were virologically suppressed at follow-up, including an infant with birthweight of only 770 g. It would be important to follow up these and other very preterm infants with HIV infection as little is known about their long-term outcomes.

Although our data seem to indicate that it is possible to eliminate intrapartum and breastfeeding transmission in this group of higher risk infants, it must be noted that 13% of our 6-week PCR results were missing. Prolonged ARV prophylaxis may also suppress viral load sufficiently to reduce sensitivity of PCR testing at 6 weeks.¹³ However, as 80% of the cohort were at least partially breast-fed, if any of these babies are subsequently shown to be HIV infected, it will be difficult to determine if the infection occurred intrapartum or through breastfeeding.

It is possible that many of our VLBW infants were over treated when they received 2 prophylactic drugs. Both the UK and US guidelines recommend single drug prophylaxis (zidovudine) when maternal viral loads are <50 copies/mL.^{14,15} Although there are little pharmacodynamic data on ARV use in preterm neonates, zidovudine and nevirapine have both been studied. Prophylactic nevirapine seems to be safe,¹⁶ while zidovudine may exacerbate anemia of prematurity and cause neutropenia.¹⁷ There has also been some speculation that zidovudine may increase the risk of necrotizing enterocolitis in preterm infants.^{18,19}

With correct care, perinatal transmission of HIV can virtually be eliminated even in the most preterm infants. Intrauterine transmission will remain a problem if mothers are not accessing ARV therapy early in their pregnancy.

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4. Appendices

Appendix I: Letters of intent

25/10/2016

Dear Professor Morrow,

Re: Research Proposal for Ethics Committee approval.

Thank you for allowing me the opportunity to submit this research proposal. The study design will be a cohort study at Groote Schuur Hospital and New Somerset hospital over a 7 month period from the 1st August 2014, to the 1st April 2015. Attached is the research synopsis, proposal as well as the data collection sheet. My supervisor for this study is Dr. Lloyd Tooke.

Kind regards

Candyce Levin

Paediatric Registrar- Red Cross War Memorial Children's Hospital

Appendix II: Ethics approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E53-46 Old Main Building
Grootes Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arafiqien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 November 2016

HREC REF: 795/2016

Dr L Tooke
Division of Neonatology
H-Floor
OMB

Dear Dr Tooke

PROJECT TITLE: HIV EXPOSED VERY LOW BIRTH WEIGHT INFANTS (MMed candidate- C Levin)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr C Levin will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 795/2016

Appendix III: Proforma Questionnaire

Maternal History

- Did mom book:
 - Yes
 - No
- Year of HIV diagnosis:
 - If been < 2 yrs give exact month and year :
- CD4 count:
 - Initial CD4 count and date if available:
 - Most recent CD4 count and date:
- Viral Load:
 - First viral load if available:
 - Most recent viral load and date:
 - Viral load within 1 week of delivery (if done)
- ARV history:
- Maternal Comorbidities:
 - Syphilis
 - TB
 - PET
 - clinical chorioamnionitis (as defined by maternal fever, tachycardia, uterine tenderness)
- Duration of ruptured membranes (hours):
 - Yes
 - Duration? :
 - No

Infant record:

- GA:
 - By U/S < 20 weeks:
 - By ballard
- Mode of delivery:
 - NVD
 - C/S in labour
 - C/S before labour
 -
- Birth Weight (g):
- HC (cm):
- Relevant Clinical signs:
- PMTCT plan:
 - NVP
 - Duration:
 - AZT
 - Duration:
 - Other:
 - Duration:
- Birth PCR result:
 - Negative
 - Positive
 - Equivocal
- Relevant medical history
 - Sepsis
 - NEC
 - Congenital infection (specify)

- Feeding history :

- 6/52 PCR result:
 - Negative
 - Positive
 - Equivocal

- Was PMTCT given correctly
 - Yes
 - No
 - Explain:

Appendix IV: Reviewer comments

Reviewer #1:

Determining in utero and intrapartum transmission rates in VLBW infants has clinical relevance. This descriptive report accomplished just that and added possible risk factors for transmission such as maternal antiretroviral coverage and viral load, and described the clinical outcome of the 5 infected infants.

I mention "possible" because the authors failed to include the non-transmitting mothers and neonatal outcomes of the uninfected babies in the analysis.

The relevance of the findings of this study as per the report is questionable. The question to ask when considering such reports for publication is "so what?" Refining the study objectives with scientific integrity that add value to the clinical evidence that guides prevention, diagnosis and treatment of HIV in this cohort, together with modest statistical assistance and extensive assistance with scientific writing, the authors should consider resubmitting as a new manuscript or submit to another journal.

Reviewer #2:

As the numbers of new infant HIV infections continues to decrease globally, this paper "HIV transmission to premature very low birth weight infants" is quite timely in providing data on remaining risk factors for mother to child transmission of HIV-1 in the presence of ART. The introduction/ background section is well written and highlights the limited information currently available regarding factors affecting transmission risk among very low birth weight HIV exposed infants.

Methods: The methods section is succinct and clear in describing the prospective follow up done over a 9 month period from August 2014- April 2015 at two tertiary referral hospitals in Western Cape, South Africa.

The Results reflect well on the excellent tertiary care provided at the two hospitals in Cape Town: the majority of VLBW babies were born by c-section prior to labor onset; birth PCRs were turned around quickly, with offering of dual prophylaxis with ZDV and NVP to those infants who were PCR negative at birth; and with 83% surviving. Of note, the overall transmission was 6.1%; and occurred among women with little or no antenatal ARVs received for PMTCT. Of note, all transmissions were in utero based on timing of first positive PCR, and no transmissions occurred among those who were seen at follow up at 6 weeks (85% seen) or at 10 weeks (38% tested). This suggests that the combined ZDV and infant NVP prophylaxis was highly effective among an extremely high risk group of neonates.

Strengths: Study design is a well-developed prospective case series with systematic complete capture of data on VLBW babies born over a 9 month period at 2 tertiary care hospitals in Cape Town. The neonatal dual ART prophylaxis intervention utilized appears highly effective with no transmissions reported among those followed through 6 weeks who were negative on their birth PCR result. The results are quite encouraging.

Relative Weaknesses:

One concern is the loss to follow up of infants by 10 weeks post-delivery where less than 40% of infants were still being observed. If possible, follow up outreach tracking of these infants is recommended to document later infant infection status.

The low transmission rates were seen in a setting of high level tertiary neonatal care being provided. In terms of generalizability, it would be of interest to also present data on newborn transmission and survival rates at non tertiary Western Cape delivery facilities for pregnant women who were not referred to the two tertiary hospitals prior to birth but then delivered VLBW infants in non specialized maternity facilities. This would give a more complete picture of the overall early HIV transmission and HIV free survival outcomes for VLBW infants in the Western Cape Province; in addition to the encouraging outcomes seen at the two tertiary facilities.

Overall well conducted prospective case series from the Western Cape, S. Africa with encouraging low early transmission rates; and also high newborn survival. Also of interest was that there were no documented transmissions from birth through 6 weeks among these VLBW infants who received dual infant ARV prophylaxis.

Reviewer #3:

Abstract:

do not use "immature" when referring to preterm delivery or premature infants

manuscript:

Please provide more information on the delivery of the HIV infected infants as well as how the gestational age at delivery at birth was determined. it is also not clear the duration of HIV treatment in the mothers (described as prophylaxis in the manuscript) for each of the infants that were HIV infected. at what gestational age was treatment initiated? a vague comment about 2,4, and 8 weeks was vaguely mentioned. it would be helpful at least to add the age at initiation of drug therapy for each of the infants that were PCR positive at D1 in the table. it is not clear if the 5 infants who were PCR positive at delivery were induced vs. spontaneous delivery? what the indications for delivery were? was the delivery vaginal or via cesarean section? if delivered by C/S what was the reason? did the mothers receive intrapartum AZT?

The majority of women were not suppressed at the time of delivery, was intrapartum AZT used at the time of delivery or C/S? The infant prophylaxis was described, but is there a recommended maternal prophylaxis for women who are not suppressed in labor at the two hospitals used for the study? How was the gestational age of the infants estimated? by US? Ballard at delivery? it appears that some infants were growth restricted based on reported gestational age and infant weights.

It also looks as there is a high loss to follow up in infants at 6 and 10 weeks? missing PCR for 42/58 infants in the last figure? is that correct?

Appendix V: Supplementary information

Background

The majority of new paediatric HIV cases results from perinatal transmission of HIV. Perinatal transmission of HIV is a result of the women passing the HIV virus to her baby either during pregnancy, labour, delivery or breastfeeding. Without ARV's the risk of perinatal HIV transmission can be as high as 45 percent. [1] This can be decreased to as low as 2% if ARV's are commenced during pregnancy and there is a choice of delivery route. [2] Vertical transmission of HIV can take place in utero, during delivery, and postnatally through breastfeeding. Vertical transmission during labour accounts for 65% of neonatal infections.[3]

One of the major risk factors and one of the strongest independent predictors for both intra-uterine and intra-partum mother-to-child transmission is a high maternal plasma and breastmilk viral load.[4, 5] Maternal viral load is of more value as a prognostic marker for transmission risk than CD4 cell number.[6] In Utero transmissions are thought to be as a result of the breakdown of the placenta, resulting in micro transfusions of viraemic maternal blood across the placenta to the fetus. In a study done in Sao Paolo, Brazil, where maternal viral loads were unavailable clinically advanced maternal HIV disease, reflecting increased viral load, was associated with a high risk of vertical transmission.[7] Placental inflammation due to genital tract infections and especially chorioamnionitis can increase in utero HIV transmission by affecting the integrity of the fetal-maternal barrier.[5] Maternal positive syphilis serology during pregnancy is not noted to increase risk of HIV from mother to child.[7] Majority of in utero transmission is thought to occur during the third trimester.[8] Seroconversion in pregnancy presents a high risk of MTCT.[3] In the ANRS French Perinatal Cohort three main factors affecting transmission were identified, high maternal plasma viral load near delivery, short duration of antenatal antiretroviral therapy and very premature delivery.[9]

Results:

Maternal data

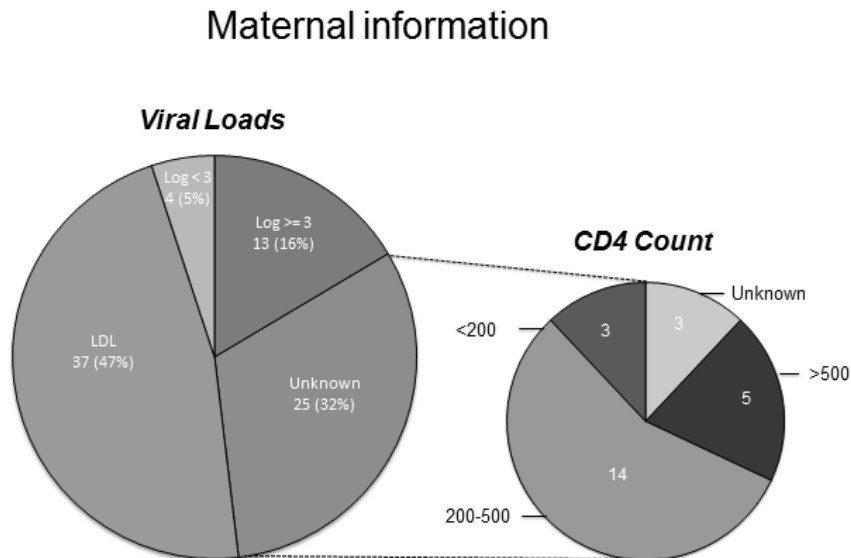
A large proportion of the mothers, 81%, were already on ARV's. Whether commenced preconception or during pregnancy. Only 10 (12.6%) were not on ARVs and majority of these mothers did not book. The remaining 5 (6.3%) ARV status was unknown. The duration of ARV treatment (**table 1**)

Table 1:

ARV's:	Number of mothers
Preconception	29
During pregnancy >1/12	28
During pregnancy <1/12	7
None	10
Unknown	5

Figure 1 illustrates the maternal viral loads. Majority of the mothers had undetectable viral loads that were either LDL (47%) or Log <3 (5%). A large percentage (32%) had unknown viral loads and therefore their CD4 counts have been included.

Figure 1:



Maternal delivery data

1. Presence of rupture of membranes

There was a total of 79 mothers, 30 (38%) had rupture of membranes and 49 (62%) had no rupture of membranes. There were 2 mother's that had confirmed chorioamnionitis, one of whose membranes had ruptured for 1 month and the other had no rupture of membranes.

The Duration of rupture of membranes is illustrated by table 2

Table 2:

Duration of rupture of membranes:	Number of mothers
< 24hrs	8
>24 hrs	10
unknown	12

2. Comorbidities

Various comorbidities that could potentially negatively affect the outcome of the infant were assessed in the mother; such as pre-eclampsia, chorioamnionitis, syphilis and tuberculosis. Nearly half of the mothers had pre-eclampsia (43%). This is not unexpected as Groote Schuur is a tertiary level obstetric unit. As mentioned above 2 mothers had confirmed chorioamnionitis. Four of the mothers had TB at some time during their pregnancy. All four had been on TB treatment for longer than two months prior to delivery and therefore no isoniazide prophylaxis for the infants was required. Only one mother had syphilis which was partially treated. Her infant had no clinical evidence of congenital syphilis.

Infant data

Most of the deliveries (57%) were by caesarean section without labour due to complications of maternal PET. The mean gestational age is 30 weeks with a mean birth weight of 1150g. The gestational age for 59 (70%) of the infants was determined using the Ballard score the remaining 30% were determined by early ultrasound (defined at GSH as an ultrasound before 20 weeks gestation). Of the 84 infants 19 (23%) had birth weights under 1000g, 25 were delivered via NVD following spontaneous preterm labour, 48 were delivered by caesarean section before labour and 11 were delivered via caesarean section in labour.

12 babies died before going home. 2 died on day 1 before a birth PCR could be performed, 1 was birth PCR positive and the remaining 9 died before their 6 week PCR. Of these 12 infants, 1 mother booked before 20 weeks, 5 were unbooked and 6 booked late. 9 (75%) of these deaths were in infants under 1000g, the smallest being 650g. The gestational ages ranged from 24-30 weeks. The overall death rate was not significantly different from our background VLBW death rate (85% vs 83%). The causes of death included; 3 confirmed sepsis (Group B streptococcus, E. Coli and K. Pneumonia), 1 presumed sepsis with a negative blood culture, 3 necrotizing enterocolitis, 2 pulmonary haemorrhage, 1 extreme prematurity at 24 weeks and 2 unexplained deaths in KMC.

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Appendix VII: PMC approval



Alan Horn

Associate Professor, Neonatal Medicine, Department of Paediatrics
Chair: Professional Master's Committee

Room 63, H46,OMB
Groote Schuur Hospital
Observatory, 7935
Cape Town, South Africa
Phone/Fax: +27 21 4046025
Email: alan.horn@uct.ac.za

19 June 2018

Dr Candyce Levin
LVNCAN001
Paediatric registrar
University of Cape Town

RE: Your Motivation for a submitting a publication of less than 2000 words for your MMed Part 3 research project.

Thank you for your letter dated 8 May 2018. You stated :

1. your article, 'HIV transmission to very low birth weight infants' was published on the 01/09/2017 in the Paediatric Infectious Disease Journal (PIDJ), which has an impact factor of 2.5.
2. The word count of the article is 1314 (excluding abstract, tables and references) including abstract, tables and references the count is 2172 words, in keeping with the journal requirements to include references in the word count.
3. Your thesis submission will include supplementary information which was included in my research (but not in the article) with a word count of 754 (excluding tables, figures and references) therefore taking the total word count to 2068.

The Professional Masters Committee considered this type of circumstance last year, and on 1 December 2018 the PMC resolved that a publication with a word count of less than 2000 words can be accepted if it complies with the other MMED requirements, as stipulated in the MMed guidelines document, and if the student provides a letter motivating for its acceptance, referring to the status of the journal and explaining why a lower word count was required. In addition, an appendix of additional information should be attached, which when considered together with the manuscript, brings the word count to at least 2000 words.

Since your motivation and publication meet these conditions, your publication and supplementary information will be accepted as meeting sufficient criteria to be considered for MMed part 3 and may be submitted for marking.

Yours sincerely

Signature Removed

/Prof Alan Horn

"Our Mission is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."